Recommendations for Complying With Over-the-Counter Monograph Procedure for Minor Changes C001: Minor Changes to Solid Oral Dosage Forms for Certain Over-the-Counter Monograph Drugs

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) at CDER-Quality-Policy@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2025
Over-the-Counter

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TABLE OF CONTENTS

Recommendations for Complying With Over-the-Counter Monograph Procedure for Minor Changes C001: Minor Changes to Solid Oral Dosage Forms for Certain Over-the-Counter Monograph Drugs Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for how requestors[2] can comply with the requirements described in Proposed Administrative Order (OTC000038) titled Over-the-Counter Monograph Procedure for Minor Changes C001: Minor Changes to Solid Oral Dosage Forms for Certain Over-the-Counter Monograph Drugs (hereinafter referred to as C001). The recommendations in this guidance are intended to assist requestors when making a minor change in the dosage form of an over-the-counter (OTC) monograph drug as described in 505G(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[3] and, if finalized, C001. Specifically, this guidance provides recommendations for demonstrating that a minor change in a solid oral dosage form from a tablet or capsule to a chewable tablet, orally disintegrating tablet (ODT), or film will not affect the safety or effectiveness of the drug. It also provides recommendations for demonstrating that such a change will not materially affect the extent of absorption or other exposure to an active ingredient in the drug in comparison to a suitable reference product.[4]

The recommendations provided in this guidance apply to nonprescription drugs marketed under section 505G of the FD&C Act, referred to as OTC monograph drugs.[5] The recommendations provided in this guidance do not apply to drugs that are the subject of an application submitted

[1] This guidance has been prepared by the Office of Pharmaceutical Quality, Office of New Drugs, and Office of Regulatory Policy in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] In § C001.2(a) of Over-the-Counter Monograph Procedure for Minor Changes C001: Minor Changes to Solid Oral Dosage Forms for Certain Over-the-Counter Monograph Drugs (hereinafter referred to as C001), FDA proposes defining *requestor* as "[a]ny person or group of persons marketing, manufacturing, processing, or developing a drug," consistent with the definition of *requestor* under section 505G(q)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(q)(3)).

[3] See 21 U.S.C. 355h(c).

[4] See C001.

[5] See definition of OTC monograph drug in section 744L(5) of the FD&C Act (21 U.S.C. 379j-71(5)).

under section 505(b) or section 505(j) of the FD&C Act[6] or biological products that are the subject of an application submitted under section 351 of the Public Health Service Act.[7]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On March 27, 2020, the President signed into law the Coronavirus Aid, Relief, and Economic Security Act (CARES Act). In addition to its other measures, the CARES Act added section 505G to the FD&C Act. Section 505G reforms and modernizes the framework for the regulation of OTC monograph drugs.[8] OTC monograph drugs may be marketed without an approved drug application under section 505 of the FD&C Act if they meet the requirements of section 505G of the FD&C Act, as well as other applicable requirements.

Under the process described in section 505G(c) of the FD&C Act, requestors can make minor changes in the dosage form of an OTC monograph drug without the issuance of an order under section 505G(b) of the FD&C Act[9] for the new dosage form if they maintain information necessary to demonstrate that the change: (1) will not affect the safety or effectiveness of the drug; and (2) will not materially affect the extent of absorption or other exposure to the active ingredient(s) in comparison to a suitable reference product.[10] The change must also be in conformity with the requirements of an applicable administrative order issued under section 505G(c)(3) of the FD&C Act.[11]

FDA is issuing proposed C001 under section 505G(c)(3) of the FD&C Act. This proposed order, if finalized, will specify the requirements that must be met for a minor change in dosage form of an OTC monograph drug from a capsule or tablet to a chewable tablet, ODT, or film.

III. GENERAL 505G(c) PRODUCT AND SUITABLE REFERENCE PRODUCT CRITERIA

Section 505G(c) of the FD&C Act allows for a minor change in the dosage form of certain drugs marketed under section 505G of the FD&C Act, without the issuance of an order under section 505G(b) of the FD&C Act adding the new dosage form to an applicable OTC monograph or otherwise finding the new dosage form to be generally recognized as safe and effective

[6] See 21 U.S.C. 355(b) and (j).
[7] See 42 U.S.C. 262.
[8] The CARES Act also added section 744M (21 U.S.C. 379j-72), among related provisions, to the FD&C Act authorizing FDA to assess and collect user fees to support OTC monograph drug activities.
[9] See 21 U.S.C. 355h(b).
[10] See section 505G(c)(1)(A) of the FD&C Act.
[11] See section 505G(c)(1)(B) of the FD&C Act.

(GRASE), when certain criteria are met. Specifically, section 505G(c)(1) of the FD&C Act permits such minor dosage form changes to an OTC monograph drug that meets applicable monograph conditions or is otherwise the subject of an order under section 505G(b) of the FD&C Act[12] provided the requestor maintains information necessary for the demonstrations described in section II above with respect to the change. Further, the change must conform to requirements of an applicable order issued under section 505G(c)(3) of the FD&C Act. Such an order specifies requirements for determining whether a particular minor dosage form change to a drug will affect the safety or effectiveness of the drug or materially affect the extent of absorption or other exposure to an active ingredient in the drug in comparison to a suitable reference product.

In issuing proposed C001 under section 505G(c)(3) of the FD&C Act, FDA proposes criteria that, if met, would allow a requestor to market a 505G(c) product[13] with a minor dosage form change from tablets or capsules to chewable tablets, ODTs, or films, without an order issued under section 505G(b) of the FD&C Act amending an applicable monograph to add the new dosage form (or otherwise finding the new dosage form to be GRASE). Such criteria include that the 505G(c) product must have the same active ingredient(s),[14] same strength, same labeled indication, and same route of administration as the suitable reference product to which it is being compared.[15] Further, in accordance with C001, if finalized, both the 505G(c) product and the suitable reference product must be orally administered, immediate-release drug products in a solid dosage form and must contain active ingredients that are systemically absorbed, highly soluble, and highly permeable.[16]

IV. INFORMATION TO SUPPORT A 505G(c) MINOR DOSAGE FORM CHANGE

Drug absorption from orally administered, immediate-release solid dosage forms is affected by the solubility and intestinal permeability of the active ingredient and the dissolution of the drug product. For highly soluble and highly permeable active ingredients with systemic absorption, FDA proposes that multimedia dissolution testing demonstrating the rapid dissolution of both the suitable reference product and the 505G(c) product is appropriate to demonstrate that the minor change in dosage form will not materially affect the extent of absorption or other exposure to the active ingredient in comparison to a suitable reference product.[17,18]

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[12] The OTC Monographs as set forth in Final Administrative Orders are available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf.

[13] In § C001.2(d) of C001, the Agency proposes defining *505G(c) product* as "[a] drug that incorporates a minor dosage form change made in accordance with the requirements of section 505G(c) and [C001]."

[14] For the purposes of selecting a suitable reference product, the *same active ingredient* includes the salt or ester form of the active ingredient.

[15] See § C001.10(b) of C001.

[16] See §§ C001.10(c) and (d) of C001.

[17] For more on the use of a scientific- and risk-based approach grounded in the biopharmaceutics classification systems, see Amidon GL, Lennernäs H, Shah VP, and Crison JR, 1995, A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharm Res, 12:413–420.

[18] See § C001.20(a) of C001.

The following sections provide recommendations for demonstrating that a dosage form change meets the requirements of C001, if finalized. The testing procedures described below are like those described in the ICH guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021)[19] but have been modified to make them appropriate for OTC monograph drugs.

Solubility and permeability are active ingredient-specific characteristics; however, dissolution is a product-specific characteristic, which may be impacted by product formulation or manufacturing. Therefore, each time a requestor makes any formulation change or makes a change in the manufacturing process related to the dosage form that is subject to C001 that could impact the dissolution profile, the drug with that change or changes will need to meet the requirements of C001, if finalized, for that dosage form to remain compliant with and permissible under section 505G(c) of the FD&C Act.

A. Solubility

An active ingredient is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 mL or less of aqueous media over the pH range of 1.2 to 6.8 at 37±1°C. The requestor should evaluate the solubility at equilibrium in at least three pH conditions, including in buffers at pH 1.2, 4.5, and 6.8.[20] Buffers should be prepared as described in the United States Pharmacopeia (USP),[21] and the pH should be verified (i.e., measured and adjusted) after addition of the active ingredient and at the end of the solubility study to ensure the solubility measurements are obtained under the specified pH. The requestor should conduct a minimum of three replicate solubility determinations for each pH over a time frame suitable to reach equilibrium using a shake-flask technique or an alternative method capable of adequately predicting the equilibrium solubility of the active ingredient. Small volumes of solubility media can be used if the available experimental apparatus will permit it. Alternatively, solubility experiments where the highest therapeutic single dose is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be used to demonstrate high solubility.

The concentration of the active ingredient in each buffer should be determined using a suitably validated method[22] that can distinguish the active ingredient from its degradation products. Samples should be filtered before analysis. Any degradation of the active ingredient should be documented. If degradation is >10%, solubility cannot be adequately determined, and the active ingredient solubility cannot be classified. The lowest measured solubility over the pH range of 1.2 to 6.8 is used to classify the active ingredient. Published peer-reviewed literature data are one way to substantiate and support solubility determinations.

[19] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[20] See USP General Chapter <1236> *Solubility Measurements* for more information on the effect of pH on solubility measurements and methods for determination of equilibrium solubility.

[21] See USP Reagents and Reference Tables for Buffer Solutions.

[22] See the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015).

B. Permeability

Active ingredient permeability can be determined by either in vivo or in vitro methods. In vivo permeability can be based on the extent of absorption derived from human pharmacokinetic studies (e.g., absolute bioavailability or mass balance). High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless the requestor maintains information to demonstrate that they are not produced before absorption (e.g., by microbial action within the gastrointestinal tract). As a scientific matter, unchanged drug in feces cannot be counted toward the extent of absorption, unless appropriate data support that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion or intestinal secretion or originates from an unstable metabolite (e.g., glucuronide, sulfate, N-oxide) that has been converted back to the parent by the action of microbial organisms.

Human in vivo data derived from published peer-reviewed literature (e.g., product knowledge and bioavailability studies) can be appropriate; however, caution should be used when relying on peer-reviewed literature as such literature might not contain the necessary details of the testing to make a judgment regarding the quality of the results.

Permeability can also be determined by validated and standardized in vitro methods using Caco-2 cells. Caco-2 epithelial cell monolayers derived from a human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation and express cell polarity with an apical brush border, tight intercellular junctions, and several active transporters as in the small intestine. However, due to a potential for low or absent expression of efflux (e.g., P-gp, BCRP, MRP2) and uptake (e.g., PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays as the sole data in support of high permeability classification is limited to passively transported drugs. If high permeability is inferred by Caco-2 cell assays, the requestor should demonstrate that permeability is independent of active transport.

When using Caco-2 cell assays for permeability determination, requestors should demonstrate suitability by establishing a rank-order relationship between experimental permeability values and the extent of drug absorption in human subjects using zero, low (<50%), moderate (50% to 84%), and high (≥85%) permeability model drugs. A sufficient number of model drugs are recommended for the validation to characterize high, moderate, and low permeability (minimum of five for each), plus a compound with proven zero permeability (see Table 1 for examples). Further, a sufficient number (minimum of three) of cell assay replicates should be employed to provide a reliable estimate of drug permeability. The established relationship should permit differentiation between low, moderate, and high permeability drugs. Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance measures and/or other suitable indicators, before and after an experiment. In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (see Table 1).

Method validation data should include a list of the selected model drugs, along with data on extent of absorption in humans (mean, standard deviation, and coefficient of variation) used to establish suitability of the method, permeability values for each model drug (mean, standard deviation, and coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95% confidence interval) with identification of the high permeability class boundary and selected high permeability model drug used to classify the active ingredient. A description of the study method, drug concentrations in the donor fluid, description of the analytical method, and equation used to calculate permeability should be recorded. Additionally, information on efflux potential (e.g., bidirectional transport data) should be recorded for a known substrate.

When conducting Caco-2 cell assays, the requestor should demonstrate passive transport of the active ingredient being tested. This can be verified using a suitable assay system that expresses known efflux transporters. For example, the requestor can demonstrate independence of measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 mL) or transport direction (efflux ratio, i.e., ratio of apparent permeability between the basolateral-to-apical and apical-to-basolateral directions <2 for the selected drug concentrations). The requestor should verify functional expression of efflux transporters by using bidirectional transport studies demonstrating asymmetric permeability of selected efflux transporter substrates (e.g., digoxin, vinblastine, rhodamine 123) at nonsaturating concentrations.

The requestor should justify the concentrations of the active ingredient used in the permeability studies. A validated Caco-2 method used for drug permeability determinations should employ conditions established during the validation and include a moderate and a high permeability model drug in the donor fluid along with the active ingredient being tested as internal standards to demonstrate consistency of the method. The requestor should choose internal standards based on compatibility with the active ingredient (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). The permeability of the internal standards can be determined following evaluation of the active ingredient in the same monolayers or monolayers in the same plate when it is not feasible to include internal standards in the same cell culture well as the active ingredient permeability evaluation. The permeability values of the internal standards should be consistent between different tests, including those conducted during method validation, and the requestor should set acceptance criteria for the internal standards and model efflux drug. The requestor should assess mean drug and internal standards recovery at the end of the test. For recoveries <80%, a mass balance evaluation should be conducted, including measurement of the residual amount of drug in the cell monolayer and testing apparatus.

Evaluation of active ingredient permeability can be facilitated by selection of a high permeability internal standard with permeability in close proximity to the moderate/high permeability class boundary. The active ingredient is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.[23] Information to support high permeability of an active ingredient (mean, standard deviation, and coefficient of variation) should include permeability data on the active ingredient, the internal standards, in vitro gastrointestinal stability information, and data supporting passive transport

[23] See § C001.2(k) of C001.

mechanism. The permeability results from Caco-2 cell assays should be discussed in the context of available data on human pharmacokinetics.

For both in vivo (i.e., mass balance studies) and in vitro approaches to demonstrating high permeability, requestors should demonstrate stability of the active ingredient in the gastrointestinal tract.[24] Stability in the gastrointestinal tract should be documented using compendial or simulated gastric and intestinal fluids. Other relevant methods can be used with suitable justification. Drug solutions should be incubated at 37ºC for a period that is representative of the in vivo contact of the active ingredient with these fluids (i.e., 1 hour in gastric fluid and 3 hours in intestinal fluid). Drug concentrations should then be determined using a suitably validated method.[25] If degradation is >10%, as a scientific matter, permeability cannot be adequately determined, and the active ingredient permeability cannot be classified.

[24] As a scientific matter, if a mass balance study demonstrates that ≥85% of the dose of the active ingredient is recovered unchanged in urine, stability in the gastrointestinal tract is considered self-evident, and additional data are not needed.

[25] See footnote 22.

Table 1. Examples of Model Drugs for Permeability Assay Method Validation

Model Drug Classification	Model Drug
High Permeability ($f_a \geq 85\%$)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability ($f_a = 50\%–84\%$)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability ($f_a < 50\%$)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide Polyethylene glycol 400 Enalaprilat
Zero Permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine

C. In Vitro Dissolution

Under C001, if finalized, requestors must demonstrate that the suitable reference product and 505G(c) product are rapidly dissolving.[26] In C001, the Agency proposes that a drug product is considered rapidly dissolving when a mean of 85 percent or more of the labeled amount of the active ingredient dissolves within 30 minutes in at least three different media across a physiological pH range, including but not limited to pH 1.2, 4.5, and 6.8 under a defined set of conditions.[27] To demonstrate rapid dissolution, the requestor should conduct comparative in vitro dissolution testing to characterize the dissolution profiles of the suitable reference product and the 505G(c) product using the following conditions:

- Apparatus: USP Apparatus 1 (basket) or USP Apparatus 2 (paddle)[28]
- Agitation: 100 revolutions per minute for basket apparatus and 50 revolutions per minute for paddle apparatus
- Volume of dissolution medium: 900 mL or less (FDA recommends the use of the volume selected for quality control dissolution testing)
- Temperature of dissolution medium: 37±1°C

Buffers should be prepared as described in the USP.[29] Solubility enhancements to the dissolution method, such as the use of organic solvents or the addition of surfactants to the dissolution media, are not appropriate for demonstrating the drug product is rapidly dissolving.[30] For gelatin capsules and tablets with gelatin coating where cross-linking has been demonstrated, the addition of enzymes to the dissolution media can be appropriate if adequately justified.[31]

The dissolution testing apparatus should conform to the requirements in USP General Chapter <711> *Dissolution* and the guidance for industry *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 — Current Good Manufacturing Practice (CGMP)* (January 2010). Selection of the testing apparatus and the testing conditions are dependent on the dosage forms being tested. Testing conditions should be appropriate for the dosage form being tested and do not need to be the same for the suitable reference product and the 505G(c) product.

If C001 becomes final, at least 12 dosage units of the suitable reference product and the 505G(c) product must be used in each dissolution medium to generate the dissolution profiles.[32] Samples should be collected at sufficient time points to characterize the dissolution profiles of the drug

[26] See § C001.20(a)(1) of C001.
[27] Ibid.
[28] See USP General Chapter <711> *Dissolution*.
[29] See footnote 21.
[30] See USP General Chapter <1092> *The Dissolution Procedure: Development and Validation.*
[31] See USP General Chapters <711> *Dissolution*, <1092> *The Dissolution Procedure: Development and Validation*, and <1094> *Capsules—Dissolution Testing and Related Quality Attributes*.
[32] See footnote 26.

products (e.g., 5, 10, 15, 20, and 30 minutes). In accordance with C001, if finalized, both the suitable reference product and the 505G(c) product must be rapidly dissolving (≥85% mean dissolved in ≤30 minutes).[33]

V. ADDITIONAL PRODUCT-SPECIFIC QUALITY CONSIDERATIONS

All 505G(c) products must meet applicable monograph conditions and other requirements for being generally recognized as safe and effective, and not misbranded, including, among other things, that the drug products be manufactured in compliance with current good manufacturing practice regulations in 21 CFR parts 210 and 211.[34] Requestors should apply the general principles described in ICH and FDA guidance documents and USP General Chapters related to pharmaceutical development and quality standards to 505G(c) products and other OTC monograph drugs, as appropriate.

All three of the dosage forms that could be marketed subject to C001, if finalized, can be vulnerable to changes in quality due to exposure to high humidity and other external factors. The container closure system of a drug must meet the requirement that container closure systems provide adequate protection against such factors.[35] For OTC monograph drugs with a minor change in dosage form, the results of testing conducted to comply with 21 CFR 211.166 must confirm the stability of the drug product in its marketed container closure system over the shelf life of the drug product.

In addition to the general recommendations above, FDA recommends the following considerations for the dosage forms that are subject to C001.

A. Chewable Tablets

Chewable tablets are intended to be chewed or crushed and then swallowed by the consumer rather than swallowed whole. Critical quality attributes for chewable tablets include, but are not limited to, hardness, disintegration, and dissolution. Additional considerations such as tablet size and taste can affect the ability or willingness of a consumer to chew the chewable tablet. Product attributes should ensure the performance of the chewable tablet for its intended use. See the guidance for industry *Quality Attribute Considerations for Chewable Tablets* (August 2018) for recommendations on critical quality attributes that should be assessed for chewable tablets.

B. Orally Disintegrating Tablets

ODTs are intended to disintegrate rapidly in the mouth on contact with saliva with no need for chewing or drinking liquids to ingest the product. Therefore, palatability and disintegration are critical quality attributes for this dosage form. The Agency recommends that ODTs have an in

[33] Ibid.

[34] See section 505G(c)(1) of the FD&C Act (21 U.S.C. 355h(c)(1)); also see 21 CFR 330.1(a) and section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).

[35] See 21 CFR 211.94(b).

vitro disintegration time of approximately 30 seconds or less using the procedure described in USP General Chapter <701> *Disintegration*.[36]

C. Films

Films for oral administration are intended to rapidly disintegrate on the tongue and incorporate the active ingredient into saliva before being swallowed. Palatability, film dimensions, film integrity, and disintegration are critical quality attributes for this dosage form. Film dimensions should be appropriate for the oral route of administration and the intended consumer population. In addition, the film should be substantial enough to maintain its integrity during manufacturing and permit handling by the consumer.

VI. PACKAGING AND RECORDKEEPING

Under section 505G(c) of the FD&C Act, a requestor must maintain information necessary to demonstrate that the minor change in dosage form will not affect the safety or effectiveness of the drug. In § C001.60(a)(1)(B) of C001, the Agency proposes that requestors must maintain information demonstrating that the packaging of 505G(c) products is consistent with the requirements described in Proposed Administrative Order OTC000037 titled Over-the-Counter Monograph Condition B001: Single-Unit or Unit-Dose Containers for Over-the-Counter Monograph Drugs in Orally Disintegrating Tablet and Film Dosage Forms (hereinafter referred to as B001), if finalized.[37] This information is necessary to demonstrate that the change in dosage form will not materially affect the extent of absorption or other exposure to the active ingredient in comparison to the suitable reference product or affect the safety or effectiveness of the drug. If B001 is finalized, OTC monograph drugs in an ODT or film dosage form that are subject to an OTC monograph identified in B001 must be packaged in single-unit or unit-dose containers as a condition for being considered generally recognized as safe and effective and not misbranded.

In B001 FDA proposes that certain OTC monograph drugs in an ODT or film dosage form must be in single-unit or unit-dose containers to address potential safety and efficacy concerns posed, in part, because these dosage forms dissolve quickly in the mouth and are designed to be more palatable than other oral dosage forms such as tablets and capsules. The palatability and rapid dissolution of ODTs and films make them more attractive to and can pose greater risks of accidental ingestion by young children. Moreover, ODTs can break apart when handled or stored in high humidity, which could result in underdosing from a multiple-unit container. Films packaged in multiple-unit containers have the potential to stick together, making it easy for a consumer to inadvertently dose more than one film at the same time.

[36] See also the guidance for industry *Orally Disintegrating Tablets* (December 2008).

[37] As proposed in § C001.60(b), if finalized, the requestor must maintain this information until at least 1 year after the expiration date of the final released batch of the 505G(c) product (see proposed § C001.60(b)(1)), or at least 3 years after distribution of the final released batch of the 505G(c) product if the batches lack expiration dating but meet the criteria described in 21 CFR 211.137(h) (see proposed § C001.60(b)(2)).

Drugs in a chewable tablet dosage form are not designed to rapidly dissolve in the mouth and do not have the same potential to break apart or stick together when handled or stored in high humidity like ODTs and films. However, chewable tablets are designed to be palatable like ODTs and films because they are intended to be chewed. Chewable tablets also have lower hardness values than other oral dosage forms such as tablets and capsules. Because of these attributes, chewable tablets can pose some of the same safety and effectiveness concerns as ODTs and films. Therefore, FDA recommends that 505G(c) products in a chewable tablet dosage form be packaged in single-unit or unit-dose containers.

As previously noted, all drug products marketed under section 505G of the FD&C Act with minor dosage form changes compliant with section 505G(c) of the FD&C Act must also be manufactured in compliance with current good manufacturing practice regulations in parts 210 and 211 so as not to render the drug adulterated under section 501(a)(2)(B) of the FD&C Act.[38] Records maintained to meet the requirements at §§ 211.180(a) and (b) are sufficient to also meet the proposed requirement at § C001.60(a)(1)(B) of C001.

FDA reminds sponsors[39] that, under section 505G(c)(2) of the FD&C Act, they are required to submit sufficient records and applicable information demonstrating that the requirements under section 505G(c) of the FD&C Act and C001, if finalized, are being met, if requested by FDA under section 704(a)(4) of the FD&C Act[40] and within 15 business days of receiving such a request, or such longer period as FDA may provide.

VII. DRUG LISTING INFORMATION

Section 510(j) of the FD&C Act[41] requires registrants to provide to FDA a list of all drugs manufactured, prepared, propagated, compounded, or processed by the registrant for commercial distribution.[42] Section 505G(e) of the FD&C Act[43] requires a sponsor who makes a change to a drug subject to section 505G, including section 505G(c), to submit updated drug listing information in accordance with section 510(j) within 30 calendar days of the date when the drug is first commercially marketed.[44]

[38] Under 21 CFR part 211, for example §§ 211.180(a) and (b), records for all components, drug product containers, closures, and labeling are required to be maintained.

[39] In § C001.2(b) of C001, FDA proposes defining *sponsor* as "[a]ny person marketing, manufacturing, or processing a drug that (1) is listed pursuant to section 510(j) of the FD&C Act; and (2) is or will be subject to an administrative order under section 505G of the FD&C Act," consistent with the definition of *sponsor* under section 505G(q)(2) of the FD&C Act (21 U.S.C. 355h(q)(2)).

[40] See 21 U.S.C. 374(a)(4).

[41] See 21 U.S.C. 360(j).

[42] See section 510(j)(1) of the FD&C Act (21 U.S.C. 360(j)(1)).

[43] See 21 U.S.C. 355h(e).

[44] Section 505G(e) of the FD&C Act also states that "a sponsor who was an order requestor with respect to an order subject to [section 505G(b)(5)(C) of the FD&C Act] (or a licensee, assignee, or successor in interest of such requestor) shall submit updated drug listing information on or before the date when the drug is first commercially marketed." This provision is not applicable to changes made under the minor dosage form changes provisions in section 505G(c) of the FD&C Act.

The Agency intends to provide more detailed information on how a sponsor should indicate that a drug product is a 505G(c) product as part of submitting drug listing information before finalizing C001.